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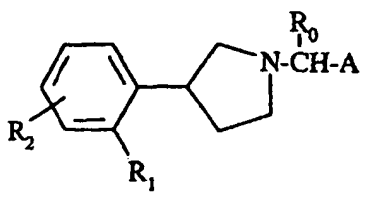
(54) Title: 1,3-DISUBSTITUTED PYRROLIDINES AS ALPHA-2-ADRENOCEPTOR ANTAGONISTS



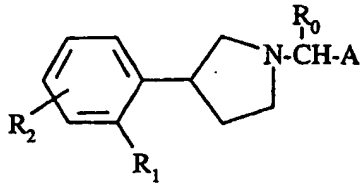
(I)

(57) Abstract: The invention provides compounds of formula (I) wherein R_0, R_1, R_2 and A are as defined in the description, and the preparation thereof. The compounds of formula (I) have high affinity as α_2 adrenoceptors and hence are useful as pharmaceuticals.

1,3-DISUBSTITUTED PYRROLIDINES AS ALPHA-2-ADRENOCEPTOR ANTAGONISTS

The present invention relates to novel 1,3-disubstituted pyrrolidines, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

More particularly the invention provides a compound of formula I



I

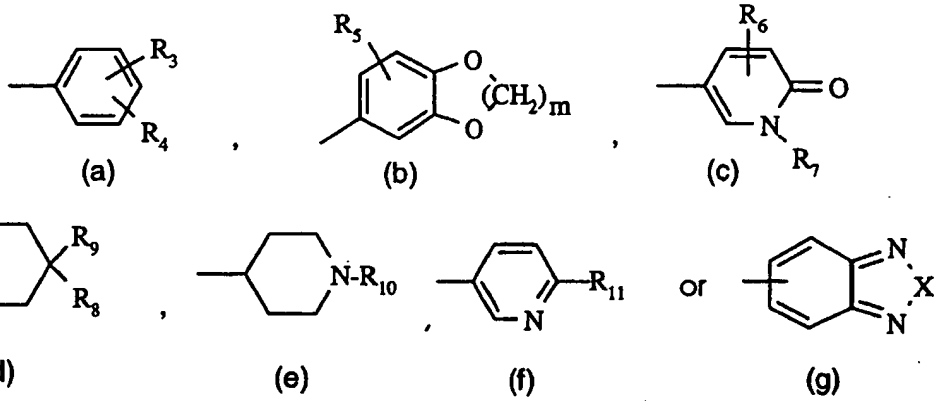
wherein

R_0 is hydrogen or (C_{1-4})alkyl,

R_1 is halogen, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{2-5})alkenyloxy, trifluoromethyl or trifluoromethoxy, and can also be hydrogen if A is a group of formula (b), (c), (f) or (g),

R_2 is hydrogen or as defined for R_1, or, when in ortho position to R_1, can also form with R_1 a methylenedioxy group, and

A is tetrahydropyran-4-yl or a group of formula



(a) (b) (c) (d) (e) (f) (g)

wherein

m is 1 to 3,

X is O, S or CH=CH,

R_3 is hydrogen, halogen, hydroxy, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy, trifluoromethyl, (C_{1-4})alkylsulfonylamino, benzyloxy, carbamoyl,

(C_{1-4})alkylcarbamoyl or di(C_{1-4})alkylcarbamoyl,

R_4 and R_5 are hydrogen, halogen, (C_{1-4})alkyl or (C_{1-4})alkoxy,

R_6 is hydrogen, halogen or (C_{1-4})alkyl,

R_7 is hydrogen, (C_{1-6})alkyl or (C_{3-7})cycloalkyl(C_{1-4})alkyl,

R_8 is hydrogen, halogen, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy, amino, (C_{2-5})alkanoylamino, benzoylamino, (C_{1-4})alkylsulfonylamino, benzylsulfonylamino,furylcarbonylamino, carbamoyl, (C_{1-4})alkylcarbamoyl or di(C_{1-4})alkylcarbamoyl, and

R_9 is hydrogen, halogen, (C_{1-4})alkyl or phenyl, or

R_8 and R_9 together are $-O-(CH_2)_m-O-$ wherein m is as defined above,

R_{10} is hydrogen, (C_{1-4})alkyl, (C_{3-6})cycloalkyl(C_{1-4})alkyl, (C_{1-4})alkylcarbonyl, (C_{3-6})cycloalkylcarbonyl, (C_{1-4})alkoxycarbonyl, benzyl, benzyloxycarbonyl, benzoyl, (C_{1-4})alkylsulfonyl, phenylsulfonyl, benzylcarbonyl, benzylsulfonyl, 2-furylcarbonylamino or N-(C_{1-4})alkyl-N-(2-furylcarbonyl)amino, and

R_{11} is hydrogen or (C_{1-4})alkoxy,

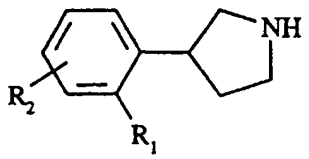
in free base or acid addition salt form.

On account of the asymmetical carbon atom(s) present in the compounds of formula I and their salts, the compounds may exist in optically active form or in form of mixtures of optical isomers, e.g. in form of racemic mixtures. All optical isomers and their mixtures including the racemic mixtures are part of the present invention.

Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

Any alkyl and alkoxy radicals are branched or straight chain radicals. They are preferably methyl or methoxy groups.

In a further aspect the invention provides a process for the production of the compounds of formula I and their salts, whereby a compound of formula II



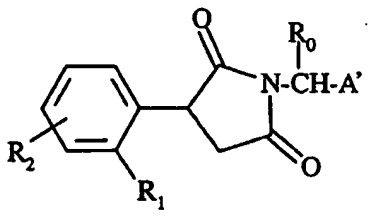
II

wherein R_1 and R_2 are as defined above, is alkylated and the resulting compound is recovered in free base form or as an acid addition salt.

The alkylation can be effected in accordance to conventional procedures, for example using an appropriate compound of formula Y-CHR_o-A, wherein R_o and A are as defined above and Y is iodine, bromine, chlorine, mesyloxy or tosyloxy, in the presence of a base and in an inert solvent, preferably at elevated temperature, e.g. as described in Example 1. Alternatively a compound R_o-CO-A, wherein R_o and A are as defined above, can be used (reductive alkylation), e.g. as described in Example 4. For the preparation of a compound of formula I wherein R_o is hydrogen, the alkylation can also be effected by acylation with an acid A-COOH, wherein A is as defined above, and subsequent reduction, e.g. as described in Example 2.

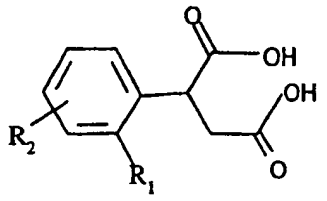
For the preparation of a compound of formula I wherein A is a group of formula (c) or (e), the substituent R_7 or R_{10} may suitably be introduced after the alkylation or acylation/reduction of the compound of formula II, e.g. as described in Example 3.

Compounds of formula I wherein A is as defined above but free from reduceable functional groups (hereinafter A'), can also be obtained by reduction of a compound of formula III



III

wherein R_o, R_1, R_2 and A' are as defined above, obtained by ring closure of a diacid of formula IV



IV

wherein R_1 and R_2 are as defined above, with an amine H_2N-CHR_o-A', wherein R_o and A' are as defined above.

Working up of the reaction mixtures obtained according to the above process and purification of the compounds thus obtained may be carried out in accordance to know procedures.

Compounds of formula I in optically pure form can be obtained from the corresponding racemates according to well-known procedures, or using optically pure starting materials, e.g. as described in Examples 2 to 5.

Acid addition salts may be produced in known manner from the free base forms and vice-versa.

The starting compounds of formulae II, IV, Y-CHR_o-A and H_2N-CHR_o-A are known or may be obtained from known compounds, using conventional procedures.

The compounds of formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro and in animals, and are therefore useful as pharmaceuticals.

In binding assays, the agents of the invention display high affinity at α_2 adrenoceptor subtypes, with selectivity to α_{2C}, as shown in a radioligand binding assay using ^{3}H-RX821002 as a ligand and membranes from CHO K1 cells expressing the recombinant human α_2 adrenoceptor subtypes. In this assay, agents of the invention exhibit pK_d values of about 6 to about 10.

In in vitro antagonist experiments using cAMP-based luciferase reporter gene assays based on transfected CHO K1 cells stably expressing the recombinant human α_2 receptors, in

presence of the α_2 agonists UK 14,304 or noradrenaline, agents of the invention act as competitive antagonists at the α_2 receptors with pK_B values of about 6 to about 9.

In vivo, the agents of the invention inhibit loxapine-induced catalepsy in rats [cf. Kalkman H.O. et al., Br. J. Pharmacol. 124:1550-1556 (1998)] at doses of about 0.3 to about 30mg/kg s.c.

Furthermore the agents of the invention inhibit amphetamine induced locomotion in rats at doses of about 0.3 to about 30mg/kg s.c. Locomotion (ambulatory activity) is measured as the number of consecutive infrared interruptions in an appropriate device during a period of 15 min. directly following s.c. injection of amphetamine (1mg/kg) or solvent (physiological saline) at t=0. The compound or the solvent are administered at t= -30 min.

In view of the above, the agents of the invention are useful as antipsychotics in the treatment of schizophrenia, in the treatment of depression (including bipolar disorders) and more generally in the treatment of any condition associated with a deficiency of noradrenaline in the central or peripheral nervous system which is compensated by α-antagonists via blockade of presynaptic α2 receptors, such as cognition deficits, Parkinson disease, drug abuse, attention deficit hyperactivity disorders, glaucoma, diabetes and erectile dysfunction.

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.1 to about 100, preferably from about 0.5 to about 100 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from yout 1 to about 500, preferably from about 1 to about 300 mg of an agent of the invention, conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

In accordance with the foregoing, the present invention also provides an agent of the invention, for use as a pharmaceutical, e.g. for the treatment of schizophrenia.

The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 0.25 to about 150, preferably from 0.25 to about 25 mg of a compound according to the invention.

For all the above indications, the preferred compounds are (R)-1-isopropyl-5-[3-(2-methoxyphenyl)pyrrolidin-1-ylmethyl]-1H-pyridin-2-one and (R)-1-(2,3,-dihydro-benzo-[1,4]dioxin-6-ylmethyl)-3-(2-methoxyphenyl)pyrrolidine. In the above-mentioned loxapine-induced catalepsy test, both compounds show with 0.3-3mg/kg s.c. a long lasting, dose-dependent inhibition of catalepsy. An oral dose of 10mg/kg produces similar inhibition as 3mg/kg s.c. In the above mentioned amphetamine-induced locomotion test, both compounds dose-dependently reduce locomotion at 0.1, 0.3 and 1mg/kg s.c. (first mentioned compound) and 1, 3 and 10mg/kg s.c. (second compound).

The preferred indications are schizophrenia and depression.

Moreover the present invention provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of any condition mentioned above.

In still a further aspect the present invention provides a method for the treatment of any condition mentioned above, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The following examples illustrate the invention. The temperatures are given in degrees Celsius and are uncorrected.

Example 1: 1-(1.4-Dioxaspiro[4.5]dec-8-ylmethyl)-3-(2-methoxyphenyl)pyrrolidine

1 g of 3-(2-Methoxyphenyl)pyrrolidine is dissolved in 60 ml of dioxane and 0.85 g NaI, followed by 1.2 ml of N,N-ethyldiisopropylamine and 1.5 g of 8-bromomethyl-1.4-dioxaspiro[4.5]decane, dissolved in 5 ml of dioxane, are added. The reaction mixture is stirred overnight at 80°, evaporated and the residue extracted with ethylacetate/2N Na_2CO_3, followed by aqueous NaCl. The combined, dried and evaporated organic phases yields an oily residue which is purified by flash chromatography on silica gel using t-butylmethylether as a solvent system providing the product as an oil. MS (EI): M^+ = 331; NMR (DMSO): 1.1 (2H, m), 1.45 (3H, m), 1.6-1.8 (5H, m), 2.15 (1H, m), 2.25 (2H, m), 2.4 (1H, t), 2.6 (2H, m), 2.8 (1H, t), 3.6 (1H, t), 3.75 (3H, s), 3.85 (4H, s), 6.9 (2H, dd), 7.15 (1H, t), 7.3 (1H, d).

Example 2: (+)-5-[3-(2-methoxyphenyl)pyrrolidin-1-ylmethyl]-1H-pyridin-2-one

10.5 g of (-)-5-[3-(2-methoxyphenyl)pyrrolidin-1-carbonyl]-1H-pyridin-2-one dissolved in 100 ml of THF are added at 0° to a suspension of 6.7 g of $LiAlH_4$ in 200 ml of THF. The temperature of the reaction mixture is allowed to reach room temperature while stirring is continued for 17 hours. Subsequently, the reaction mixture is hydrolysed with NH_4Cl solution and filtered. The filtrate is evaporated and partitioned between CH_2Cl_2 and 1N Na_2CO_3, followed by aqueous NaCl. The combined organic phases are dried and evaporated and the resulting oil purified by flash chromatography on silica gel using CH_2Cl_2/MeOH 9/1 as solvent system providing the product as an oil: $[\alpha_D^{25}]$ = + 31.4° (c=1.0, EtOH); MS (EI): M^+ = 284; NMR (DMSO): 1.75 (1H, m), 2.15 (1H, m), 2.4 (1H, t), 2.6 (2H, m), 2.8 (1H, t), 3.3-3.4 (2H, m), 3.6 (1H, m), 3.75 (3H, s), 6.3 (1H, d), 6.85-6.95 (2H, m), 7.15 (1H, t), 7.2 (1H, s), 7.25 (1H, d), 7.45 (1H, dd), 11.4 (1H, s).

The starting (-)-5-[3-(2-methoxyphenyl)pyrrolidin-1-carbonyl]-1H-pyridin-2-one is prepared as follows:

6.26 g of 6-hydroxynicotinic acid are suspended in 300 ml of DMF and 9.3 g N,N'-dicyclohexylcarbodiimide, followed by 6.1 g of 1-hydroxybenztriazole are added. After 30 minutes of stirring at room temperature, 8.0 g of (-)-3-(2-methoxyphenyl)pyrrolidine, dissolved in 45 ml of DMF, is added to the resulting solution and stirring continued

overnight. Dicyclohexylurea is filtered off, the resulting filtrate evaporated and the residue partitioned between ethylacetate and 2N HCl, followed by aqueous NaCl solution. The combined organic phases are dried and evaporated and the resulting residue purified by flash chromatography on silica gel using CH_2Cl_2/MeOH/conc. aqueous NH_4OH 95/4.5/0.5 as solvent system providing the product as a white foam: $[\alpha_D^{25}]$ = - 34.7° (c=1.0, EtOH); MS (CI): MH^+ = 299; NMR (DMSO): 2.05 (1H, m), 2.15 (1H, m), 3.45-3.9 (8H, m), 6.35 (1H, d), 6.9-7.05 (2H, m), 7.25 (2H, m), 7.65 (1H, dd), 7.75 (1H, s), 11.9 (1H, s).

Example 3: (+)-1-Isopropyl-5-[3-(2-methoxyphenyl)pyrrolidin-1-ylmethyl]-1H-pyridin-2-one and (+)-2-Isopropoxy-5-[3-(2-methoxyphenyl)pyrrolidin-1-ylmethyl]-1H-pyridine

9.75 g of (+)-5-[3-(2-methoxyphenyl)pyrrolidin-1-ylmethyl]-1H-pyridin-2-one (example 2) are dissolved in 170 ml of toluene. 14.2 g of Na_2CO_3, followed by 6.9 ml of isopropyl-iodide are added to the solution which is stirred at 100° overnight. Subsequently, another 3.4 g of isopropyliodide are added and stirring continued for additional 17 hours. The reaction solution is extracted with water and the combined organic phases dried and evaporated resulting in an oily residue which is purified by flash chromatography on silica gel using CH_2Cl_2/MeOH/conc. aqueous NH_4OH 95/4.5/0.5 as solvent system which provides (+)-1-Isopropyl-5-[3-(2-methoxyphenyl)pyrrolidin-1-ylmethyl]-1H-pyridin-2-one {$[\alpha_D^{25}]$ = +19.7° (c=1.0, EtOH); MS (CI): MH^+ = 327; NMR (DMSO, 120°): 1.3 (6H, d), 1.95 (1H, m), 2.3 (1H, m), 2.7-3.4 (4H, m), 3.6-3.8 (3H, m), 3.8 (3H, s), 5.0 (1H, q), 6.35 (1H, d), 6.9-7.0 (2H, m), 7.2 (1H, t), 7.3 (1H, m), 7.4 (1H, m), 7.6 (1H, m)} and (+)-2-Isopropoxy-5-[3-(2-methoxyphenyl)pyrrolidin-1-ylmethyl]-1H-pyridine {$[\alpha_D^{25}]$ = + 22.8° (c=1.0, EtOH); MS (EI): M^+ = 326; NMR (DMSO): 1.3 (6H, d), 1.75 (1H, m), 2.15 (1H, m), 2.4 (1H, t), 2.65 (2H, m), 2.8 (1H, t), 3.5-3.65 (3H, m), 3.75 (3H, s), 5.2 (1H, m), 6.7 (1H, d), 6.85-6.95 (2H, m), 7.15 (1H, t), 7.3 (1H, d), 7.6 (1H, m), 8.05 (1H, s)}

Example 4: (+)-1-(2,3-Dihydrobenz[1.4]dioxin-6-methyl)-3-(2-methoxyphenyl)pyrrolidine

1.77 g of (-)-3-(2-methoxyphenyl)pyrrolidine, followed by 1.8 g of 2,3-dihydrobenz[1.4]-dioxine-6-carbaldehyde are dissolved in 40 ml of MeOH. 1.26 g of $NaCNBH_3$ is added and the reaction mixture stirred during 3 hours at room temperature. The solvent is evaporated and the residue partitioned between ethylacetate and water. The organic phases are

combined, dried and evaporated and the resulting oily residue purified by flash chromatography on silica gel using ethylacetate/hexane 1/9 as solvent system. The product is obtained as an oil which is transformed into the hydrochloride salt: mp 201-202°; $[\alpha_D^{20}]$ = + 9.7° (c=1.0, MeOH); MS (ES): MH^+ = 326; NMR (DMSO/NaOD): 1.7 (1H, m), 2.15 (1H, m), 2.35 (1H, q), 2.6-2.7 (2H, m), 2.8 (1H, t), 3.45 (1H,q), 3.55 (1H, q), 3.75 (3H, s), 4.2 (4H, s), 6.75-6.95 (5H, m), 7.15 (1H, t), 7.25 (1H, d).

Example 5: (-)-2-[1-(2,3-Dihydrobenzo[1.4]dioxin-6-ylmethyl)pyrrolidin-3-yl]phenol

450 mg of (-)-2-pyrrolidin-3ylphenol, followed by 520 mg of of 2,3-dihydrobenz[1.4]-dioxine-6-carbaldehyde are dissolved in 10 ml of MeOH. The pH is adjusted to 5.5 by addition of acetic acid and the reaction solution is stirred for 2 hours, before 443 mg of $NaCNBH_3$ is added in portions. Stirring is continued overnight, the solvent subsequently evaporated and the residue purified by flash chromatography on silica gel with CH_2Cl_2/EtOH/conc. aqueous NH_4OH 95/4.5/0.5 which provides the product as an oil: $[\alpha_D^{20}]$ = - 35.6° (c=0.75, EtOH); MS (EI): M^+ = 311; NMR (DMSO): 1.7 (1H, m), 2.2-2.4 (2H, m), 2.6 (1H, t), 2.75 (1H, dd), 2.95 (1H, t), 3.4 (1H, m), 3.6 (2H, q), 4.25 (4H, s), 6.65 (1H, t), 6.7 (1H, d), 6.75-6.85 (3H, m), 6.95-7.05 (2H, m).

The starting (-)-5-[3-(2-methoxyphenyl)pyrrolidin-1-carbonyl]-1H-pyridin-2-one is prepared as follows:

500 mg of (-)-3-(2-methoxyphenyl)pyrrolidine are dissolved in 12 ml of CH_2Cl_2, 8.5 ml of a 1 M BBr_3 solution in CH_2Cl_2 is addded dropwise at 0° and stirring continued overnight. The reaction mixture is poured on 1N Na_2CO_3 solution, extracted with CH_2Cl_2 and the organic phases washed with brine, dried, evaporated and purified by flash chromatography on silica gel with CH_2Cl_2/EtOH/conc. aqueous NH_4OH 88/10.8/1.2 providing the product as an oil: MS (EI): M^+ = 163; NMR (DMSO, 120°): 1.85 (1H, m), 2.2 (1H, m), 2.8 (2H, broad), 2.95-3.05 (2H, m), 2.2-2.4 (2H, m), 3.5 (1H, m), 6.7 (1H, t), 6.8 (1H, d), 7.05 (1H, m), 7.1 (1H, dd).

Example 6: 1-Benzyl-3-(5-chloro-2-methoxyphenyl)pyrrolidine

730 mg of 1-benzyl-3-(5-chloro-2-methoxyphenyl)pyrroline-2,5-dione are dissolved in 2 ml of acetylchloride and stirred at room temperature for 24 hours. The acetylchloride is evaporated, the residue dried and added to a suspension of 295 mg of $LiAlH_4$ in 15 ml of ether. The reaction mixture is stirred during 30 minutes, hydrolyzed, filtered and partitioned between CH_2Cl_2 and 2N Na_2CO_3, followed by aqueous NaCl. The combined, dried and evaporated organic phases yield an oil which is purified by flash chromatography using ethylacetate/hexane 1/1 providing the product as a colorless oil: MS (CI): MH^+ = 302; NMR (DMSO): 1.7 (1H, m), 2.2 (1H, m), 2.4-2.8 (5H, m), 3.6 (2H, q), 3.75 (3H, s), 6.95 (1H, d), 7.15-7.35 (7H, m).

The starting 1-Benzyl-3-(5-chloro-2-methoxyphenyl)pyrroline-2,5-dione is prepared as follows:

1.0 g of 2-(5-chloro-2-methoxyphenyl)succinic acid is suspended in 50 ml of xylene, 0.47 ml of benzylamine is added and the mixture refluxed for 8 hours with separation of water. The solvent is evaporated and the residue taken up in ethylacetate and extracted with 2N HCl, followed by 2N NaOH and aqueous NaCl. The organic layer is dried, filtered and the solvent evaporated. The dried residue is purified by flash chromatography using t-butylmethylether/hexane 1/1 providing the amorphous product: MS (EI): M^+ = 329; NMR (DMSO): 2.65 (1H, dd), 3.1 (1H, dd), 3.45 (3H, s), 4.2 (1H, dd), 4.6 (2H, s), 7.0 (1H, d), 7.25-7.4 (7H, m).

The following compounds of formula I wherein R_0, R_1, R_2 and A have the significancies indicated in the table are produced analogously to Example 1. The compounds marked "A" under "Remarks" are preferably produced analogously to Example 2, the compounds marked "B" preferably analogously to Example 4 or 5, and the compounds marked "C" preferably analogously to Example 3.

Ex.	R_0	R_1	R_2	A	$[\alpha_D]$	MS	Re-marks
7	H	OMe	H	a; R_3=p-OH, R_4=H	+/-	284 (MH^+/FAB)	

8	"	"	"	a; R_3=R_4=H	+/-	268 (MH^+/FAB)	1
9	"	"	"	a; R_3=o-Cl, R_4=H	+/-	301 (M^+/EI)	
10	"	O-CH-$(CH_3)_2$	"	a; R_3=R_4=H	+/-	295 (M^+/EI)	
11	"	O-CH_2-CH=CH_2	"	"	+/-	293 (M^+/EI)	
12	"	OMe	"	a; R_3=m-OMe, R_4=H	+/-	298 (MH^+/FAB)	
13	"	"	"	a; R_3=p-$C(CH_3)_3$; R_4=H	+/-	323 (M^+/EI)	
14	"	"	"	d; R_8=R_9=H	+/-	273 (M^+/EI)	
15	"	"	"	b; m=1, R_5=H	+/-	311 (M^+/EI)	
16	Me	"	"	a; R_3=R_4=H	+/-	281 (M^+/EI)	
17	H	"	"	a; R_3=3-OMe, R_4=5-OMe	+/-	327 (M^+/EI)	A
18	"	"	"	d; R_8=benzyl-sulfonylamino, R_9=H	+/-	456 (M^+/EI)	
19	"	"	"	d; R_8=OMe, R_9=H	+/-	303 (M^+/EI)	
20	"	"	"	e; R_{10}= -$COOC(CH_3)_3$	+/-	375 (MH^+/ES)	
21	"	"	"	e; R_{10}=benzoyl	+/-	379 (MH^+/ES)	
22	"	"	"	d; R_8=OH, R_9=Me	+/-	303 (M^+/EI)	

23	"	"	"	d; R_8=OH, R_9=phenyl	+/-	366 (MH^+/ES)	
24	"	"	"	d; R_8=benzoyl-amino, R_9=H	+/-	393 (MH^+/ES)	
25	"	"	"	d; R_8=-NHCOMe, R_9=H	+/-	331 (MH^+/ES)	
26	"	"	"	a; R_3=p-CH_2OH, R_4=H	+/-	298 (MH^+/ES)	A
27	"	"	"	a; R_3=p-F, R_4=H	+/-	285 (M^+/EI)	
28	"	"	"	a; R_3=m-$NHSO_2$-Me, R_4=H	+/-	361 (MH^+/ES)	
29	"	"	"	a; R_3=p-$CON(CH_3)_2$, R_4=H	+/-	338 (M^+/EI)	
30	"	"	5-F	a; R_3=R_4=H	+/-	285 (M^+/EI)	2
31	"	"	5-Me	"	+/-	281 (M^+/EI)	3
32	"	"	5-OMe	"	+/-	297 (M^+/EI)	
33	"	"	4-OMe	"	+/-	297 (M^+/EI)	
34	"	"	3-OMe	"	+/-	297 (M^+/EI)	
35	"	"	H	d; R_8=-NHCO-2-furyl, R_9=H	+/-	382 (M^+/EI)	
36	"	"	"	f; R_{11}=H	+/-	268 (M^+/EI)	A
37	"	"	"	c; R_6=H, R_7=Me	+/-	298 (M^+/EI)	A
38	"	"	"	d; R_8=R_9=F	+10.3° (c=1/EtOH)	309 (M^+/EI)	

39	"	"	6-OMe	a; R_3=R_4=H	+/-	297 (M^+/EI)	
40	"	"	H	c; R_6=H, R_7=cyclo-propylmethyl	+19.3° (c=1/EtOH)	339 (MH^+/ES)	A
41	"	"	3-Me	a; R_3=R_4=H	+/-	282 (MH^+/ES)	
42	"	"	H	a; R_3=3-OMe, R_4=4-OMe	+25.0° (c=0.5/EtOH)	328 (MH^+/CI)	
43	"	"	"	c; R_6=H, R_7=propyl	-18.4° (c=0.9/EtOH)	327 (MH^+/ES)	A
44	"	"	"	a; R_3= m-CON(CH_3)$_2$; R_4=H	+19.3° (c=1/EtOH)	338 (M^+/EI)	
45	"	-O-CH_2-O-		a; R_3=R_4=H	+/-	281 (M^+/EI)	
46	"	OMe	H	tetrahydropyran-4-yl	+11.4° (c=1/EtOH)	275 (M^+/EI)	A
47	"	"	"	g; X=O, X-containing ring in 2,3	+/-	309 (M^+/EI)	B
48	"	"	"	g; X=O, X-containing ring in 3,4	+20.2° (c=0.4/EtOH)	326 (MH^+/CI)	
49	"	"	"	b; m=3, R_5=H	+24.5° (c=1/EtOH)	340 °	
50	"	"	"	g; X= CH=CH, X-containing ring in 3,4	+11.7° (c=0.5/EtOH)	320 (MH^+/ES)	
51	"	H	"	b; m=2, R_5=H	+/-	296 (MH^+/ES)	B
52	"	Me	"	"	+/-	309 (M^+/EI)	B

53	"	H	4-OMe	c; R_6=H, R_7=isopropyl	+/-	326 (M^+/EI)	C
54	"	"	4-Cl	"	+/-	331 (MH^+/ES)	C
55	"	OMe	5-F	"	+14.5° (c=1/EtOH)	345 (MH^+/ES)	C
56	"	"	6-OMe	b; m=2, R_5=H	+/-	356 (MH^+/ES)	B
57	"	OCF_3	H	"	+/-	380 (MH^+/ES)	B
58	"	CF_3	H	"	+/-	364 (MH^+/ES)	B
59	"	H	4-CF_3	"	+/-	363 (M^+/EI)	B
60	"	OMe	3-Me	c; R_6=H, R_7=isopropyl	+/-	341 (MH^+/ES)	C
61	"	"	5-Me	b; m=2, R_5=H	+/-	340 (MH^+/ES)	4, B
62	"	H	4-F	c; R_6=H, R_7=isopropyl	+32.0° (c=1/EtOH)	315 (MH^+/ES)	C
63	"	F	H	"	+/-	315 (MH^+/EI)	C

Me = methyl

1: Mp = 138° (hydrogenfumarate)

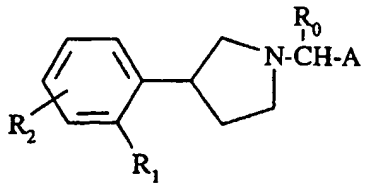
2: Mp = 142-144° (hydrogenfumarate)

3: Mp = 146-149° (hydrogenfumarate)

4: Mp = 164-149° (hydrochloride)

Claims

1. A compound of formula I



I

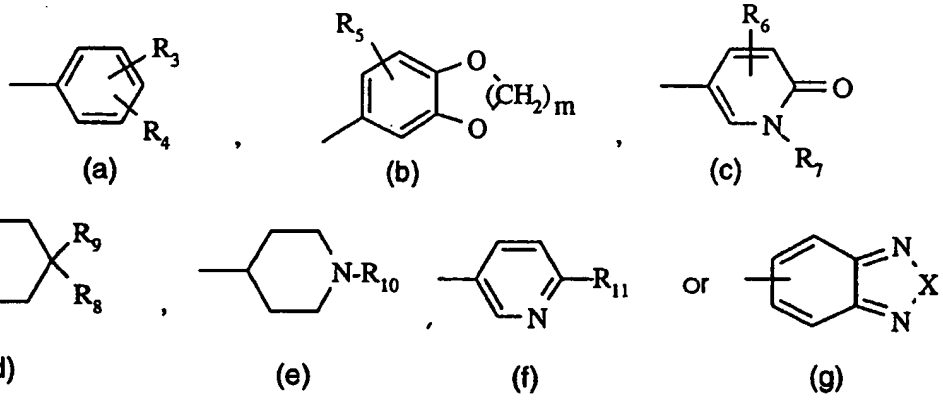
wherein

R_0 is hydrogen or (C_{1-4})alkyl,

R_1 is halogen, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{2-5})alkenyloxy, trifluoromethyl or trifluoromethoxy, and can also be hydrogen if A is a group of formula (b), (c), (f) or (g),

R_2 is hydrogen or as defined for R_1, or, when in ortho position to R_1, can also form with R_1 a methylenedioxy group, and

A is tetrahydropyran-4-yl or a group of formula



(a) (b) (c) (d) (e) (f) (g)

wherein

m is 1 to 3,

X is O, S or CH=CH,

R_3 is hydrogen, halogen, hydroxy, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy, trifluoromethyl, (C_{1-4})alkylsulfonylamino, benzyloxy, carbamoyl, (C_{1-4})alkylcarbamoyl or di(C_{1-4})alkylcarbamoyl,

R_4 and R_5 are hydrogen, halogen, (C_{1-4})alkyl or (C_{1-4})alkoxy,

R_6 is hydrogen, halogen or (C_{1-4})alkyl,

R_7 is hydrogen, (C_{1-6})alkyl or (C_{3-7})cycloalkyl(C_{1-4})alkyl,

R_8 is hydrogen, halogen, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy, amino, (C_{2-5})alkanoylamino, benzoylamino, (C_{1-4})alkylsulfonylamino, benzylsulfonylamino,furylcarbonylamino, carbamoyl, (C_{1-4})alkylcarbamoyl or di(C_{1-4})alkylcarbamoyl, and

R_9 is hydrogen, halogen, (C_{1-4})alkyl or phenyl, or

R_8 and R_9 together are -O-$(CH_2)_m$-O- wherein m is as defined above,

R_{10} is hydrogen, (C_{1-4})alkyl, (C_{3-6})cycloalkyl(C_{1-4})alkyl, (C_{1-4})alkylcarbonyl, (C_{3-6})cycloalkylcarbonyl, (C_{1-4})alkoxycarbonyl, benzyl, benzyloxycarbonyl, benzoyl, (C_{1-4})alkylsulfonyl, phenylsulfonyl, benzylcarbonyl, benzylsulfonyl, 2-furylcarbonylamino or N-(C_{1-4})alkyl-N-(2-furylcarbonyl)amino, and

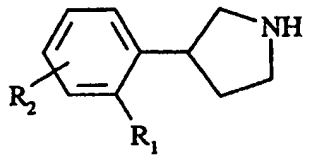
R_{11} is hydrogen or (C_{1-4})alkoxy,

in free base or acid addition salt form.

2. (S)-1-Isopropyl-5-[3-(2-methoxyphenyl)pyrrolidin-1-ylmethyl]-1H-pyridin-2- one in free base or acid addition salt form.

3. (S)-1-(2,3-Dihydrobenzo[1,4]dioxin-6-ylmethyl)-3-(2-methoxyphenyl)pyrrolidine in free base or acid addition salt form.

4. A process for the production of a compound of formula I as defined in claim 1, which comprises alkylating a compound of formula II



II

wherein R_1 and R_2 are as defined in claim 1, and recovering the resulting compound in free base form or as an acid addition salt.

5. A compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

6. A compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of any state responsive to α2 adrenoceptor antagonists.

7. A pharmaceutical composition comprising a compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

8. The use of a compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the treatment of any state responsive to α2 adrenoceptor antagonists.

9. The use of a compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of any state responsive to α2 adrenoceptor antagonists.

10. A method for the treatment of any state responsive to α2 adrenoceptor antagonists, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form.

INTERNATIONAL SEARCH REPORT

Int. nal A. ion No
PCT/EP 01/00861

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/06 C07D401/06 C07D207/06 C07D405/12 C07D413/06
C07D403/06 A61K31/4025 A61P25/18 A61P25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 62, no. 4, 1965 Columbus, Ohio, US; abstract no. 3995b, XP002164442 Compounds of formula IV wherein RR' = OCH2O and OCH2CH2O abstract & A.V.EL'TSOV ET AL: "N-Aralkyl derivatives of phenylpyrrolidines" ZH. OBSHCH. KHIM., vol. 34, no. 10, 1964, pages 3344-3351, ---	1,3,5,7
X	WO 00 03714 A (CARLSSON ARVID ;SONESSON CLAS AAKE (SE); WATERS ROSS NICHOLAS (SE)) 27 January 2000 (2000-01-27) claim 1 --- -/--	1,5,7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 April 2001	03.05.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Johnson, C

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 18475 A (UPJOHN CO) 29 October 1992 (1992-10-29) claim 1; example 78	1,5,7
Y	examples S-18,,S-39; table 1	6,8-10
A	AHN, KYO HAN ET AL: "N-Substituted 3-arylpyrrolidines: potent and selective ligands at the serotonin 1A receptor" BIOORG. MED. CHEM. LETT. (1999), 9(10), 1379-1384 , XP004164896 Examples 3, 8a, 8b, 8c, Table 1	1
Y		6,8-10
A	US 5 185 364 A (DEBERNARDIS JOHN F ET AL) 9 February 1993 (1993-02-09) example 49	1,5-10

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/EP 01/00861

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8 and 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

RNATIONAL SEARCH REPORT

Information on patent family members

In nal Application No
PCT/EP 01/00861

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0003714 A	27-01-2000	AU 5456899 A	07-02-2000
WO 9218475 A	29-10-1992	AU 653837 B	13-10-1994
		AU 1986992 A	17-11-1992
		CA 2105666 A	18-10-1992
		EP 0641320 A	08-03-1995
		FI 934575 A	15-10-1993
		JP 6509561 T	27-10-1994
		KR 196888 B	15-06-1999
		MX 9201730 A	01-08-1993
		NO 933715 A,B,	15-10-1993
		US 5462947 A	31-10-1995
		US 5594024 A	14-01-1997
US 5185364 A	09-02-1993	CA 1338894 A	04-02-1997
		DE 68908392 D	16-09-1993
		DE 68908392 T	10-02-1994
		EP 0325964 A	02-08-1989
		EP 0396620 A	14-11-1990
		ES 2059828 T	16-11-1994
		JP 2673024 B	05-11-1997
		JP 3502325 T	30-05-1991
		WO 8906534 A	27-07-1989
		US 5089519 A	18-02-1992
		US 5140039 A	18-08-1992